

# PATENT COOPERATION TREATY

# PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
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**EINGEGANGEN**  
Vossius & Partner

17. Dez. 2004

Frist  
bearb.: 14.1.1F lg

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

REGISTERED MAIL

Date of mailing  
(day/month/year)

15/12/2004

Applicant's or agent's file reference  
H2216 PCT S3

7.1. He+SSP

**PAYMENT DUE**

within 30 ~~days~~/days  
from the above date of mailing

International application No.  
PCT/EP2004/009114

International filing date  
(day/month/year)

20/07/2004

Applicant

TRANSGENE S.A.

1. This International Searching Authority

- (i) considers that there are 19 (number of) inventions claimed in the international application covered by the claims indicated ~~below~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~ on the extra sheet:

- (ii) ☒ has carried out a partial international search (see Annex) ☐ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:  
see annex

- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

EUR 1.550,00 x 18 = EUR 27.900,00  
Fee per additional invention      number of additional inventions      total amount of additional fees

Or, \_\_\_\_\_ x \_\_\_\_\_ = \_\_\_\_\_

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☐ Claim(s) Nos. \_\_\_\_\_ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority



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Authorized officer

Maria Brandt

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1

claims 1-11,15-41 as far as they relate to any of the  
specific combinations of IL-2 with IL-7  
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Inventions 2-7

claims 1-11,15-41 as far as they relate to any of the  
specific combinations of IL-2 with any of  
IL-15, IL-18, IL-21, IL-27, IL-31, or IFNgamma  
---

Invention 8

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-7  
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Invention 9

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-15  
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Invention 10

claims 1-41  
as far as they relate to fusion proteins comprising IL-18  
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Invention 11

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-21  
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Invention 12

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-27  
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Invention 13

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-31  
---

Inventions 14-19

claims 1-11,15-41 as far as they relate to any of the specific combinations of IFNgamma with

- (8.1.) IL-15
- (8.2.) IL-18
- (8.3.) IL-21
- (8.4.) IL-27
- (8.5.) IL-31
- (8.6.) IL-7

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The present set of claims lacks unity within the meaning of R. 13.2. PCT.

The unifying concept of the application as filed is a fusion protein comprising two cytokines (claim 1). More specifically claimed are fusion proteins comprising any two of IL-2, IL-7, IL-15, IL-18, IL-21, IL-27, IL-31, and IFN-gamma (claim 7).

The cited prior art (EP158198, Rock et al., EP225579, EP288809, EP816510, W094/21792) discloses several examples of fusion proteins composed of two different cytokines. In view of these documents, the concept of linking two cytokines as required by claim 1 is not new and therefore cannot provide the special technical concept or feature as required by of R. 13.2 PCT.

The technical problem solved by the present application is the provision of further fusion proteins comprising cytokines. The solution are the fusion proteins as defined in the claims. In view of the cited prior art, these further fusion proteins are not linked by common special technical features.

Inventions 1-7 and 14-19, respectively are not linked by special technical features according to R. 13.2. PCT.

Fusion proteins with IL-2 have been known (e.g. IFNg-IL-2, IL-2 - IFNg, IL-2-GM-CSF, IL-2 - IL-6, and IL-2 - IL-2). Therefore, the group of inventions unified by the presence of IL-2 does not meet the requirements of R. 13.2 EPC, and each fusion protein based on IL-2 constitutes an individual invention. Likewise, because IFNg fusion proteins were already known, any further IFNg based fusion protein constitutes an independent invention.

In total there are 19 independent groups of inventions.

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
- see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 158 198 A (TAKEDA CHEMICAL INDUSTRIES LTD) 16 October 1985 (1985-10-16) <span style="float:right">✓✓</span>  the whole document	1,2,5-7, 17-19, 29-31, 34-36
X	ROCK F ET AL: "OVEREXPRESSION AND STRUCTURE-FUNCTION ANALYSIS OF A BIOENGINEERED IL-2/IL-6 CHIMERIC LYMPHOKINE" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 5, no. 6, September 1992 (1992-09), pages 583-591, XP000983961 ISSN: 0269-2139 abstract <span style="float:right">✓✓</span>	1,2,5-7, 17-19, 29-31, 34-36
X	EP 0 225 579 A (SEARLE & CO) <span style="float:right">✓✓</span> 16 June 1987 (1987-06-16)  page 8; claim 8	1,2,5-7, 17-19, 29-31, 34-36
X	EP 0 288 809 A (HOECHST AG) <span style="float:right">✓✓</span> 2 November 1988 (1988-11-02) the whole document  ----- -/-	1-5

☒ X

Further documents are listed in the continuation of box C.

☒ X

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*8\* document member of the same patent family

**Annex to Form PCT/ISA/206  
COMMUNICATION RELATING TO THE RESULTS  
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No  
**PCT/EP2004/008114**

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 816 510 A (TORAY RESEARCH CENTER INC ; TORAY INDUSTRIES (JP)) 7 January 1998 (1998-01-07) the whole document ✓ ✓	1-5
X	WO 94/21792 A (VIAGENE INC) 29 September 1994 (1994-09-29) ✓ ✓	1-9, 15-20, 22, 26-31, 34-36, 38,40 19-23
Y	pages 10,13,29; claims 1,9,11,17	
Y	WO 98/40498 A (SULLIVAN DANIEL M ; US ARMY (US); ANGLADE EDDY (US); CSAKY KARL G (US)) 17 September 1998 (1998-09-17) figure 1 ✓ ✓	19-21
Y	WO 99/36440 A (HAWKINS ROBERT EDWARD ; UNIV BRISTOL (GB); WHITTINGTON HAYLEY ANN (GB)) 22 July 1999 (1999-07-22) claim 27 ✓ ✓	19-21
Y	WO 98/08947 A (US HEALTH) 5 March 1998 (1998-03-05) ✓ ✓  pages 16,19,44	1-11, 15-38, 40,41
Y	KAUFMANN A.M. ET AL: "Comparison of cytokines and CD80 for enhancement of immunogenicity of cervical cancer cells" IMMUNOBIOLOGY, vol. 202, no. 4, October 2000 (2000-10), pages 339-352, XP009040509 GERMANY abstract ✓ ✓	1-9, 15-38, 40,41
Y	KONDO M ET AL.: "Enhancement of Interleukin-2 induced lymphokine-activated killer activity by Interleukin-7 against autologous human renal cell carcinoma" ONCOLOGY, vol. 55, no. 6, November 1998 (1998-11), pages 588-593, XP009040510 SWITZERLAND abstract ✓ ✓  ----- -/--	1-9, 15-38, 40,41

**Annex to Form PCT/ISA/206  
COMMUNICATION RELATING TO THE RESULTS  
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No  
**PCT/EP2004/008114**

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>JU D W ET AL: "Adenovirus-mediated combined suicide gene and interleukin-2 gene therapy for the treatment of established tumor and induction of antitumor immunity." JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY. 1998, vol. 124, no. 12, 1998, pages 683-689, XP002307305 ISSN: 0171-5216 abstract</p>	22,23
Y	<p>US 6 552 005 B1 (MILLER C RYAN ET AL) 22 April 2003 (2003-04-22) the whole document</p>	23
Y	<p>WO 93/20849 A (UNIV TEXAS) 28 October 1993 (1993-10-28) cited in the application the whole document</p>	10,11
Y	<p>WO 99/60128 A (LEMBACH KENNETH J ; SHANAFELT ARMEN B (US); JESMOK GARY (US); BAYER AG) 25 November 1999 (1999-11-25) cited in the application the whole document</p>	10,11
Y	<p>SHANAFELT ARMEN B ET AL: "A T-cell-selective interleukin 2 mutein exhibits potent antitumor activity and is well tolerated in vivo" NATURE BIOTECHNOLOGY, vol. 18, no. 11, November 2000 (2000-11), pages 1197-1202, XP002307306 ISSN: 1087-0156 cited in the application the whole document</p>	10,11

# Patent Family Annex

Information on patent family members

International Application No

PCT/EP2004/008114

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0158198	A	16-10-1985	WO 8504420 A1	10-10-1985
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EP 0225579	A	16-06-1987	US 4935233 A	19-06-1990
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EP 0288809	A	02-11-1988	DE 3712985 A1	03-11-1988
			AR 242991 A1	30-06-1993
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**Patent Family Annex**  
Information on patent family members

International Application No  
PCT/EP2004/008114

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			TR	200003354 T2	21-03-2001
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			US	2004175357 A1	09-09-2004

## Important Information

### general

- the **claims cannot be changed** at this point in the procedure, the transmitted report is **not** the ISR (see Art. 19 PCT)
- non-payment does not lead to a **loss of rights**, a new procedure will be started on entry into the regional or national phase
- any payments have to be effected **directly** to this ISA (account details on separate sheets), payments to other entities will not be accepted
- in case of a **total of more than 2 inventions** found: when paying please **specify exactly** which claims should be searched
- an **extension of the set time limit** may be granted, however, the total number of days **shall not exceed 45 days** (Rule 40.3 PCT). It has to be requested in writing (preferably faxed) and must be received by this ISA within the first time limit, i.e. 30 days calculating from the date of mailing.

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- only payments in EUR are accepted, no equivalents in other currencies
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### payments under protest according to Rule 40 PCT:

- the protest will **not be accepted** without a payment of additional search fee(s)
- the protest has to be **accompanied by a technical reasoning**
- no **protest fee** needs to be paid yet, only additional search fee(s)

## Account Details

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